MORPHINE SULFATE - morphine sulfate injection, solution
Barr Laboratories, Inc.

Preservative-Free
Ampul
Fliptop Vial
Protect from light
CII
Rx only

DESCRIPTION

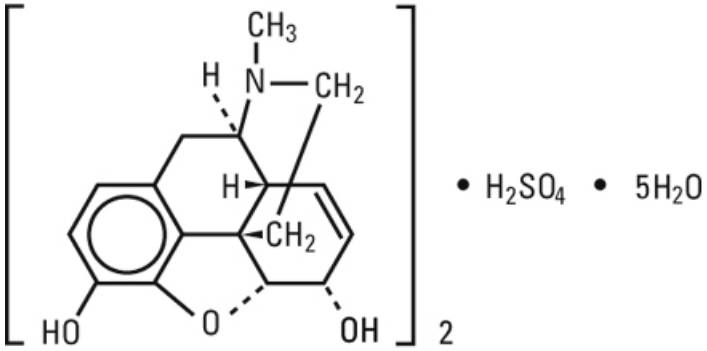
Preservative-free Morphine Sulfate Injection, USP is a sterile, nonpyrogenic, isobaric solution of morphine sulfate in water for injection.

Each mL contains morphine sulfate, pentahydrate 0.5 mg or 1 mg and sodium chloride 9 mg. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. The pH is 5.0 (2.5 to 6.5). The osmolarity of the 0.5 mg/mL and 1 mg/mL solutions is 310 and 312 mOsmol/liter (calc.), respectively. Preservative-Free Morphine Sulfate Injection, USP is oxygen sensitive.

The solution contains no antioxidant, bacteriostat or antimicrobial agent and is intended as a single-dose injection to provide analgesia via the intravenous, epidural or intrathecal routes. Each ampul and vial is intended for SINGLE USE ONLY. Discard unused portion. DO NOT HEAT-STERILIZE. Do not use the Injection if its color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate.

Morphine, the most important alkaloid of opium, is classified pharmacologically as a narcotic analgesic.

Morphine Sulfate, USP (pentahydrate) is chemically designated 7, 8-didehydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2:1) (salt), pentahydrate, a white crystalline powder, soluble in water. It has the following structural formula:



Sodium Chloride, USP is chemically designated NaCI, a white crystalline compound freely soluble in water.

CLINICAL PHARMACOLOGY

Morphine exerts its primary effects on the central nervous system and organs containing smooth muscle. Pharmacologic effects include analgesia, drowsiness, alteration in mood (euphoria), reduction in body temperature (at low doses), dose-related depression of respiration, interference with adrenocortical response to stress (at high doses), reduction in peripheral resistance with little or no effect on cardiac index and miosis.

Morphine, as other opioids, acts as an agonist interacting with stereospecific and saturable binding sites/receptors in the brain, spinal cord and other tissues. These sites have been classified as μ receptors and are widely distributed throughout the central nervous system being present in highest concentration in the limbic system (frontal and temporal cortex, amygdala and hippocampus), thalamus, striatum, hypothalamus, midbrain and laminae I, II, IV and V of the dorsal horn in the spinal cord. It has been postulated that exogenously administered morphine exerts its analgesic effect, in part, by altering the central release of neurotransmitter from afferent nerves sensitive to noxious stimuli. Peripheral threshold or responsiveness to noxious stimuli is unaffected leaving monosynaptic reflexes such as the patellar or the Achilles tendon reflex intact.

Autonomic reflexes are not affected by epidural or intrathecal morphine, however morphine exerts spasmogenic effects on the gastrointestinal tract that result in decreased peristaltic activity.

Central nervous system effects of intravenously administered morphine sulfate are influenced by ability to cross the blood-brain barrier.

The delay in the onset of analgesia following epidural or intrathecal injection may be attributed to its relatively poor lipid solubility (i.e., an oil/water partition coefficient of 1.42), and its slow access to the receptor sites. The hydrophilic character of morphine may also explain its retention in the CNS and its slow release into the systemic circulation, resulting in a prolonged effect.

Nausea and vomiting may be prominent and are thought to be the result of central stimulation of the chemoreceptor trigger zone. Histamine release is common; allergic manifestations of urticaria and, rarely, anaphylaxis may occur. Bronchoconstriction may occur either as an idiosyncratic reaction or from large dosages.

Approximately one-third of intravenous morphine is bound to plasma proteins. Free morphine is rapidly redistributed in parenchymatous tissues. The major metabolic pathway is through conjugation with glucuronic acid in the liver. Elimination half-life is approximately 1.5 to 2 hours in healthy volunteers. For intravenously administered morphine, 90% is excreted in the urine within 24 hours and traces are detectable in urine up to 48 hours. About 7-10% of administered morphine eventually appears in the feces as conjugated morphine.
Peak serum levels following epidural or intrathecal administration of *preservative-free* morphine sulfate injection are reached within 30 minutes in most subjects and decline to very low levels during the next 2 to 4 hours. The onset of action occurs in 15 to 60 minutes following epidural administration or intrathecal administration; analgesia may last up to 24 hours. Due to this extended duration of action, sustained pain relief can be provided with lower daily doses (by these two routes) than are usually required with intravenous or intramuscular morphine administration.

INDICATIONS AND USAGE

Preservative-free morphine sulfate injection is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

CONTRAINDICATIONS

Morphine sulfate injection is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.
Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

WARNINGS

Morphine sulfate injection administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.
FACILITIES WHERE MORPHINE SULFATE INJECTION IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.
SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.
Morphine sulfate may be habit forming. (See DRUG ABUSE AND DEPENDENCE.)

PRECAUTIONS

General

Morphine sulfate injection should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial/intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis).
Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.
It is recommended that administration of *preservative-free* morphine sulfate injection by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.
Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization, consideration should be given to risks inherent in urethral catheterization, (e.g., sepsis), when epidural or intrathecal administration is considered, especially in the perioperative period.
Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.
Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.
Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

Drug Interactions

Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy
Teratogenic effects—*Pregnancy Category C.* Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.
Nonteratogenic effects. Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Labor and Delivery
Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.
Epidurally and intrathecally administered morphine readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that *epidural* administration has little or no effect on the relief of labor pain. However, studies have suggested that in most cases 0.2 to 1 mg of morphine *intrathecally* provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr, for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

Nursing Mothers
Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The most serious side effect is respiratory depression. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (see WARNINGS and OVERDOSAGE). Even without clinical evidence of ventilatory inadequacy, a diminished CO_2 ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.
While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and an increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.
Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10 to 20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see PRECAUTIONS). Pruritus, nausea/vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).
Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see DRUG ABUSE AND DEPENDENCE).
Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as urticaria, wheals and/or local tissue irritation may occur.
In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE HYDROCHLORIDE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
Morphine sulfate injection is a Schedule II controlled substance.

Abuse
Morphine has recognized abuse and dependence potential.

Dependence
Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Pregnancy-Nonteratogenic Effects.)

OVERDOSAGE
Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone hydrochloride (see package insert for full prescribing information) should be administered intravenously, simultaneously with respiratory resuscitation. *As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary.* Patients should be closely observed for evidence of renarcotization. *Note: Respiratory depression may be delayed in onset up to 24 hours* following epidural or intrathecal administration. In painful conditions, reversal of narcotic effect may result in acute onset of pain and release of catecholamines. Careful administration of naloxone may permit reversal of side effects without affecting analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

DOSAGE AND ADMINISTRATION
Preservative-free morphine sulfate injection is intended for intravenous, epidural or intrathecal administration.

Intravenous Administration
Dosage: The initial dose of morphine sulfate should be 2 mg to 10 mg/70 kg of body weight. Patients under the age of 18; no information available.

Epidural Administration
PRESERVATIVE-FREE MORPHINE SULFATE INJECTION SHOULD BE ADMINISTERED EPIDURALLY ONLY BY PHYSICIANS EXPERIENCED IN THE TECHNIQUES OF EPIDURAL ADMINISTRATION AND WHO ARE THOROUGHLY FAMILIAR WITH THE LABELING. IT SHOULD BE ADMINISTERED ONLY IN SETTINGS WHERE ADEQUATE PATIENT MONITORING IS POSSIBLE. RESUSCITATIVE EQUIPMENT AND A SPECIFIC ANTAGONIST (NALOXONE HYDROCHLORIDE INJECTION) SHOULD BE IMMEDIATELY AVAILABLE FOR THE MANAGEMENT OF RESPIRATORY DEPRESSION AS WELL AS COMPLICATIONS WHICH MIGHT RESULT FROM INADVERTENT INTRATHECAL OR INTRAVASCULAR INJECTION. (NOTE: INTRATHECAL DOSAGE IS USUALLY 1/10 THAT OF EPIDURAL DOSAGE)
PATIENT MONITORING SHOULD BE CONTINUED FOR AT LEAST 24 HOURS AFTER EACH DOSE, SINCE DELAYED RESPIRATORY DEPRESSION MAY OCCUR.
Proper placement of a needle or catheter in the epidural space should be verified before *preservative-free* morphine sulfate injection is injected. Acceptable techniques for verifying proper placement include: a) aspiration to check for absence of blood or cerebrospinal fluid, or b) administration of 5 mL (3 mL in obstetric patients) of UNPRESERVED 1.5% Lidocaine and Epinephrine (1:200,000) Injection and then observe the patient for lack of tachycardia (this indicates that vascular injection has *not* been made) and lack of sudden onset of segmental anesthesia (this indicates that intrathecal injection has *not* been made).
Epidural Adult Dosage: Initial injection of 5 mg in the lumbar region may provide satisfactory pain relief for up to 24 hours. If adequate pain relief is not achieved within one hour, careful administration of incremental doses of 1 to 2 mg at intervals sufficient to assess effectiveness may be given. No more than 10 mg/24 hr should be administered.
Thoracic administration has been shown to dramatically increase the incidence of early and late respiratory depression even at doses of 1 to 2 mg.
For continuous infusion an initial dose of 2 to 4 mg/24 hours is recommended. Further doses of 1 to 2 mg may be given if pain relief is not achieved initially.
Aged or debilitated patients—Administer with extreme caution (see PRECAUTIONS). Doses of less than 5 mg may provide satisfactory pain relief for up to 24 hours.
Epidural Pediatric Use: No information on use in pediatric patients is available.

Intrathecal Administration

NOTE: INTRATHECAL DOSAGE IS USUALLY 1/10 THAT OF EPIDURAL DOSAGE.

PRESERVATIVE-FREE MORPHINE SULFATE INJECTION SHOULD BE ADMINISTERED INTRATHECALLY ONLY BY PHYSICIANS EXPERIENCED IN THE TECHNIQUES OF INTRATHECAL ADMINISTRATION AND WHO ARE

THOROUGHLY FAMILIAR WITH THE LABELING. IT SHOULD BE ADMINISTERED ONLY IN SETTINGS WHERE ADEQUATE PATIENT MONITORING IS POSSIBLE. RESUSCITATIVE EQUIPMENT AND A SPECIFIC ANTAGONIST (NALOXONE HYDROCHLORIDE INJECTION) SHOULD BE IMMEDIATELY AVAILABLE FOR THE MANAGEMENT OF RESPIRATORY DEPRESSION AS WELL AS COMPLICATIONS WHICH MIGHT RESULT FROM INADVERTENT INTRAVASCULAR INJECTION. **PATIENT MONITORING SHOULD BE CONTINUED FOR AT LEAST 24 HOURS AFTER EACH DOSE, SINCE DELAYED RESPIRATORY DEPRESSION MAY OCCUR.** RESPIRATORY DEPRESSION (BOTH EARLY AND LATE ONSET) HAS OCCURRED MORE FREQUENTLY FOLLOWING INTRATHECAL ADMINISTRATION.

Intrathecal Adult Dosage: A single injection of 0.2 to 1 mg may provide satisfactory pain relief for up to 24 hours. (CAUTION: THIS IS ONLY 0.4 TO 2 ML OF THE 5 MG/10 ML CONTAINER OR 0.2 TO 1 ML OF THE 10 MG/10 ML CONTAINER OF *PRESERVATIVE-FREE MORPHINE SULFATE INJECTION*.) DO NOT INJECT INTRATHECALLY MORE THAN 2 ML OF THE 5 MG/10 ML CONTAINER OR 1 ML OF THE 10 MG/10 ML CONTAINER. USE IN THE LUMBAR AREA ONLY IS RECOMMENDED. Repeated intrathecal injections of *preservative-free* morphine sulfate injection are not recommended. A constant intravenous infusion of naloxone hydrochloride, 0.6 mg/hr, for 24 hours after intrathecal injection may be used to reduce the incidence of potential side effects.

Aged or debilitated patients—Administer with extreme caution (see PRECAUTIONS). A lower dosage is usually satisfactory.

Repeat Dosage: If pain recurs, alternative routes of administration should be considered, since experience with repeated doses of morphine by the intrathecal route is limited.

Intrathecal Pediatric Use: No information on the use in pediatric patients is available.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless solution is clear and container is undamaged. Discard unused portion.

HOW SUPPLIED

Preservative-free Morphine Sulfate Injection, USP is supplied in cartons of five 10 mL amber ampuls or vials as follows:

NDC No.	**Package**	**Concentration (mg/mL)**	**Total Morphine (mg/10 mL)**
0555-1127-10	Ampul	0.5	5
0555-1128-10	Ampul	1	10
0555-1129-10	Fliptop Vial	0.5	5
0555-1130-10	Fliptop Vial	1	10

Contains no preservatives. Discard unused portion. **Do not heat-sterilize.**

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing. Protect from light. Store in carton until time of use.

Revised: March 2007 (v.1)

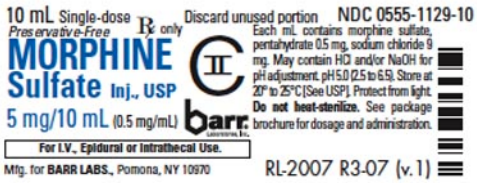
EN-1442

Manufactured by Hospira, Inc., Lake Forest, IL 60045 for

BARR LABORATORIES, INC., Pomona, NY 10970

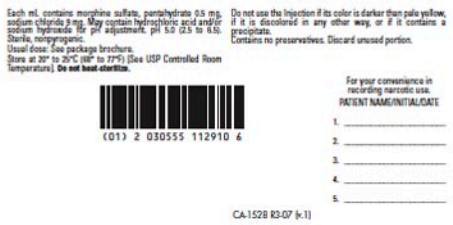
LABEL NDC 0555-1129-10

RL-2007



CARTON NDC 0555-1129-10

CA-1528



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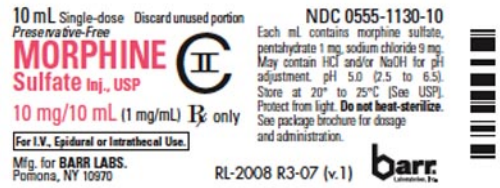

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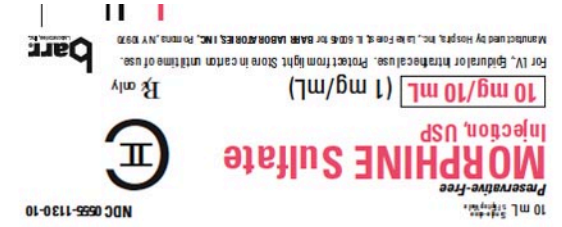

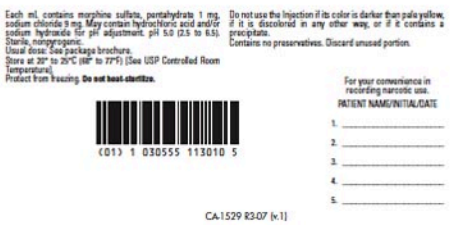

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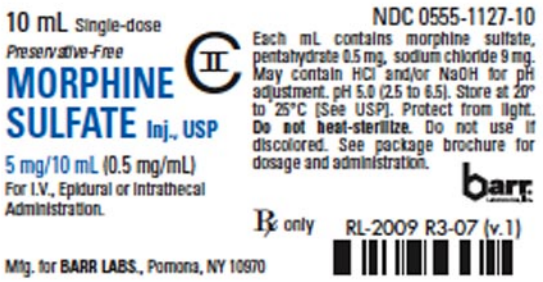

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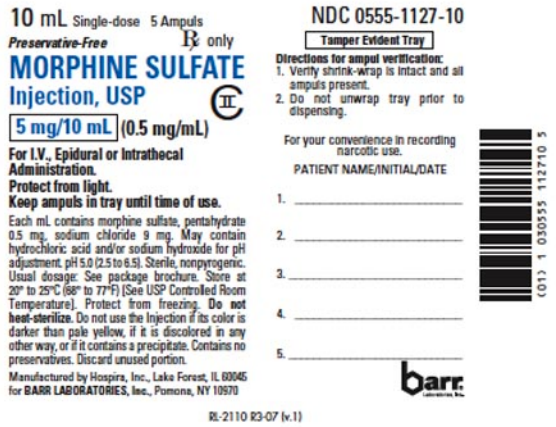

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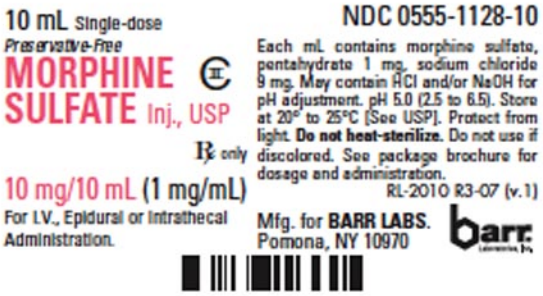
RL-2010



CARTON NDC 0555-1128-10
RL-2111

10 mL Single-dose 5 Ampuls

Preservative-Free

NDC 0555-1128-10

MORPHINE SULFATE
Injection, USP

10 mg/10 mL (1 mg/mL)

For I.V., Epidural or Intrathecal Administration.
Protect from light.
Keep ampuls in tray until time of use.

℞ only

Each mL contains morphine sulfate, pentahydrate 1 mg, sodium chloride 9 mg. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. pH 5.0 (2.5 to 6.5). Sterile, nonpyrogenic. Usual dosage: See package brochure. Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing. **Do not heat-sterilize.** Do not use the Injection if its color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate. Contains no preservatives. Discard unused portion.

Manufactured by Hospira, Inc., Lake Forest, IL 60045
for **BARR LABORATORIES, INC.**, Pomona, NY 10970

Tamper Evident Tray

Directions for ampul verification:
1. Verify shrink-wrap is intact and all ampuls present.
2. Do not unwrap tray prior to dispensing.

For your convenience in recording narcotic use.

PATIENT NAME/INITIAL/DATE

1. _____
2. _____
3. _____
4. _____
5. _____

barr

(01) 1 030555 112810 2

RL-2111 R3-07 (v.1)